REMARKS

Applicant notes with appreciation the thoroughness of the examination embodied in the Paper dated December 8, 2006 and the opportunity to distinguish the pending claims over the prior art of record. Claims 1-42 are pending in the subject application; claims 1, 2, 4-9, 11, 13, and 41 are presently under consideration; and claims 3, 10, 12, 14-40, and 42 are withdrawn from consideration. Claims 1, 2, 4-9, 11, 13, and 41 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 1, 2, 4-9, 11, 13, and 41 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Claims 1, 7, 8, 11, 13, and 41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Remarks Directed to Drawings

Amended drawings of figure 9 in compliance with 37 CFR 1.121(d) are submitted along with this response.

Remarks Directed to Rejection of Claims 1, 2, 4-9, 11, 13, and 41 under 35 U.S.C. § 112, First Paragraph, Written Description

Withdrawal of the rejection of claims 1, 2, 4-9, 11, 13, and 41 under 35 U.S.C. § 112, first paragraph, written description, is respectfully requested for at least the following reasons. Independent claims 1, 11, and 41 have been amended to include the limitation "a gene encoding primate Hpr." This amendment is fully supported by the original disclosure *inter alia* at p. 14, lines 1-4.

A complete nucleic acid sequence for Hpr in recombinant form is presented in the instant application as Seq. ID No. 28. (p. 34, lines 16-17; Figures 10, 11.) Therefore, the instant application provides sufficient written description of recombinant Hpr.

Further, Applicant presents a complete nucleic acid sequence for human Hpr as Seq. ID No. 28. (p. 34, lines 16-17; Figure 11.) The gene encoding full length Hpr, or a truncation thereof, is only found in the primates: humans, gorillas, baboons, mandrills, chimpanzees, and sooty mangabeys. Lugli, EB et al, *Molecular & Biochemical Parasitology*, (2004); 138:9–20. Of these, only humans, baboons, and chimpanzees possess full length Hpr. *Id.* Further, these Hpr genes possess high sequence homology. *Id.* Previously, Hpr was detected in genes resulting in termination of transcription in chimpanzees. Smith et al, *Science*, (1995); 268:284-286. More recent studies by Lugli contradict those results and identify full length Hpr in chimpanzees as well. Thus, the total number of species of full-length primate Hpr genes is three. As the court in *Regents* stated: "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Regents of the Univ. of Calif. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997). This standard is precisely met by the instant specification. The description by nucleotide and amino acid sequence of the cDNA for Hpr recites "structural features common to the members of the genus" given the high homology between the Hpr genes in primates. *Id.* Further, the nucleotide and amino acid sequences described recite "features [that] constitute a substantial portion of the genus" of which there exist only three members. The court in *Regents* likened a similar satisfactory number of species to that which satisfies the enablement requirement. As such, description is readily met for a genus with a full one third of

the total number of species expressly described, particularly given the high degree of sequence identity between members of the genus of primate Hpr genes.

Moreover, the recitation of the term Hpr is sufficient to describe the genus of primate Hpr genes with merely three species. This is similar to the generic term halogen found to be sufficient to describe the members of the chemical halogens. *Bigham v. Godtfredsen*, 857 F.2d 1415, 1417 (Fed. Cir. 1988) ("[t]he generic term halogen comprehends a limited number of species, and ordinarily constitutes a sufficient written description of the common halogen species.")

The instant specification further provides adequate support for small interfering RNA as a therapeutic agent such as a drug or a prodrug. The specification defines drug as "compounds used as a medicine to treat a disease, disease system, or undiagnosed pain." (p. 11, lines 1-2.) Compounds used as medicine are not limited to small molecules, but include as therapeutic agents "to treat a disease" such as genes defined in the instant specification to be "an isolated nucleic acid molecule of greater than twenty nucleotides." (p. 8, lines 1-2.) siRNAs and miRNAs are defined as "21-23 base, double strand, complementary RNA to preclude translation into functional proteins. (p. 9, lines 1-2) G. Hutvágner et al., *Science* 297, 2056-2060 (2002) (incorporated by reference p. 9, line 5); S.M. Hammond et al., Nat. Rev. Genet. 2, 110-119 (2001) (incorporated by reference p. 9, line 3). As such, drugs and prodrugs are well defined by the subject specification to fully encompass siRNA and miRNA. Examples of typical siRNAs are provided in the instant specification by Hutvagner et al (incorporated by reference p. 9, line 5). Further, the use of siRNA to modulate gene expression is described by Sharp, P, *Genes Dev*, (2001) 15:485–490 (incorporated by reference p. 9, line 4).

Moreover, siRNA and miRNA function to degrade mRNA or inhibit translation of an mRNA, these molecules regulate the level of downstream protein function, thus, functioning as drugs to "treat a disease." (p. 11, lines 1-2.) For example, RNAi has been developed to treat infection by hepatitis B or C (Zamore, P, *Nat Med*, (2003) 9:266-7; Yokota, T, *EMBO Rep*, (2003) 4:602-8), for the treatment of HIV infection (Michienzi, A, *Ann N Y Acad Sci*, (2003) 1002:63-71), autoimmune hepatitis (Song E, et al, *Nat Med*, (2003) 9:347-51), malaria (Mohmmed, A, *Biochem Biophys Res Commun*, (2003) 309:506-11), and numerous tumor types (Yin, JQ, *J Exp Ther Oncol*, (2003) 3:194-204; Butz, K, *Oncogene*, (2003) 22:5938-45; Chen, Y, *Cancer Res*, (2003) 63:4801-4; Howard, K, *Nat Biotechnol*, (2003) 21:1441-6). Each of these therapies was known to a person having ordinary skill in the art at the time of filing the subject application.

"Related to a therapeutic agent," as in claim 9, further represents an RNA molecule sufficient to promote RNAi that complements the action of a drug or prodrug delivered in tandem with the drug or prodrug by the inventive organism. For example, the therapeutic agent hypoxanthine-guanine phosphoribosyltransferase (HGPRT), is used as an improved therapeutic agent for the conversion of the prodrug allopurinol for the treatment of cancer. Trudeau et al (2001) *Hum Gene Ther*, 12(13), 1673-1680 (incorporated by reference p. 13, line 13). Inventive siRNA molecules related to cancer treatment are well known in the art and are described by Yin, JQ, *J Exp Ther Oncol*, (2003) 3:194-204; Butz, K, *Oncogene*, (2003) 22:5938-45; Chen, Y, *Cancer Res*, (2003) 63:4801-4; Howard, K, *Nat Biotechnol*, (2003) 21:1441-6. Thus, the inventive single therapeutic delivery system is capable of delivering both a therapeutic agent and an siRNA related to the therapeutic agent to target the same disease in the same cell type.

A written description need not, and should not, disclose all "art-recognized equivalents." *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1561 (Fed Cir. 1991). Each of the above described therapies, as well as the nucleotide sequences that have been effective in models of these therapies, are known and obvious to one having ordinary skill in the art. As such, the instant specification, through express definition and illustration, and as judged by the knowledge of the common practitioner in the art, conveys more than adequate written description to illustrate that Applicant had possession of the invention as of the filing date.

In light of the above remarks, it is respectfully submitted that the instant specification provides support for claims 1, 2, 4-9, 11, 13, and 41 so as to convey to persons having ordinary skill in the art that Applicant had possession of the invention consistent with the requirements of 35 U.S.C. § 112, first paragraph.

Remarks Directed to Rejection of Claims 1, 2, 4-9, 11, 13, and 41

under 35 U.S.C. § 112, First Paragraph, Enablement

Withdrawal of the rejection of claims 1, 2, 4-9, 11, 13, and 41 under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement is respectfully requested for at least the following reasons. Independent claims 1 and 11 are currently amended to include the limitation "a gene encoding primate Hpr; said gene further comprising an inducible promoter and encoding a lysosomal targeting sequence." This amendment is fully supported by the original disclosure *inter alia* at p. 14, lines 1-4; p. 8, lines 14-16; p. 13, lines 2-6; Table 1; p. 34, lines 3-7.

The instant specification teaches how a gene encoding Hpr is operative in the subject invention. The instant specification teaches that a "gene is generally under the control of an

appropriate promoter, which may be inducible, repressible, or constitutive." (p. 8, lines 14-16.) A non-limiting example of a promoter responsive to an induction species is taught by the instant specification. As depicted in Figure 1, a construct containing a gene encoding Hpr is under the control of a Tet inducible promoter (PARP*). The inventive organism constitutively expresses TetR that represses expression of the Hpr gene. (p. 20, lines 6-7.) Introduction of the inducer tetracycline removes TetR from the promoter removing the repression and allowing selectively timed expression of the Hpr gene leading to lysis of the organism. (p. 20, lines 7-11.) Thus, the instant specification teaches a concrete example of how the inclusion of recombinant Hpr protein in the Trypanosome uses a promoter to upregulate the expression of the Hpr protein.

The instant specification further teaches concrete examples of how the expressed Hpr protein leads to lysis of the Trypanosome. Example 3 teaches that the recombinant Hpr gene "contains a lysosome targeting sequence." (p. 34, line 4.) An example of a functional 43 amino acid targeting sequence is taught by Alexander et al, 2002 (incorporated by reference p. 34, line 7). Introduction of recombinant genetic material to single cell organisms is well known in the art. As taught by the instant specification, Hpr functions to lyse the Trypanosome following localization to the lysosome. (p. 34, line 3.) Therefore, the instant specification teaches the introduction of a gene encoding Hpr under the control of the inducible PARP* promoter that results in the production of a Hpr protein that is targeted to the lysosome yielding lysis of the host Trypanosome.

The system taught by the instant specification is independent of the ability of the Trypanosome to endocytose Hpr for lysis because the Hpr is produced within the Trypanosome itself. As such, the example of *Trypanosoma brucei rhodensiense*, which demonstrates poor endocytosis of serum Hpr (Shimamura et al (2001) Mol. Biocehm. Parasitol., 115:227-237) will

by readily lysed by Hpr encoded by *rhodensiense* itself completely bypassing any requirement for endocytosis. Thus, the instant specification teaches methods for circumventing the endocytic requirement of *rhodensiense* allowing Hpr to lyse this species of Trypanosome as well as *brucei*. A skilled artisan readily recognizes that the instant specification teaches production of a Typanosome containing recombinant Hpr protein stably produced, and no level of undue experimentation is required to practice the instant invention.

Further, drugs and prodrugs encompass genes encoding nucleic molecules greater than 20 nucleotides in length. *Supra*. Packaging such molecules into Typansosmes is taught by the instant specification *inter alia* Examples 1-3. Trpyanosomes are "transfected with an expression cassette" encoding host genome integration genes and a gene encoding lysosome targeted Hpr. (p. 5, lines 1-24 to p. 6, lines 1-2.) Methods of cell transfection are well known in the art and do not require undue experimentation for an ordinary practitioner to practice in the instant invention.

Further, as explained above, the number of primate Hpr genes claimed in the subject application is only three. Given the high homology between these genes combined with the high level of skill in the art of library screening and cloning, it is well within the normal skill in the art to isolate and use any species of primate Hpr gene.

The instant specification provides adequate teaching of infection of a host cell followed by lysis mediated by Hpr. Applicant respectfully suggests that Examiner intends to state Hpr mediated lysis of the Trypanosome organism as opposed to "lysis of the host cell mediated by Hpr." (paper date 12/08/2006, p. 11.) The instant specification teaches that Trypanosoma organisms naturally infect "myoblast, fibroblast, and macrophages through interaction with gp83-TSA." (p. 4, lines 1-2; Villalta et al. (2001)(incorporated by reference, p. 4, line 2.)

Further, Example 5 provides detailed teaching of infection of human myocardial cells and Example 6 provides detailed teaching of an *in vivo* mouse model whereby the period and method of tetracycline administration are both detailed. Moreover, the expression of the PARP* expression system is taught to be increased 10^3-10^4 –fold range (p. 20, lines 9-11; Wirtz et al., (1999) (incorporated by reference p. 20, line 11).

Examples 5 and 6 are prophetic in language style yet provide detailed teaching of how to make and use the instant invention. "Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications." MPEP 608.01(p). "[A] specification need not contain a working example . . . ." *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The court in *Borkowski* went on to hold that an application providing a sufficient "jumping off" point for which a practitioner may use the invention is sufficient to satisfy the enablement requirement. *Id.* Additionally, the court in *In re Strahilevitz* held that a prophetic example is sufficient to satisfy the enablement requirement. 668 F.2d 1229 (C.C.P.A 1982). The instant specification teaches numerous details including particular cell types, and infected organisms, as well as methods of detecting positively infected cells by the use of GFP. (Example 5.) The instant specification provides examples similarly detailed to those in *Borkowski* and *Strahilevitz*, and thus, satisfies the enablement requirement.

Independent claims 1, 13, and 41 are currently amended to include the limitations that the gene is regulated by an inducible promoter and encodes an Hpr protein that further comprises a lysosomal targeting sequence. These amendments are fully supported by the specification as filed *inter alia* p. 8, lines 14-16; p. 13, lines 2-6; Table 1; p. 34, lines 3-7. As claimed, the Hpr gene is under the control of an inducible promoter and is, therefore, not constitutively expressed. Lysis of the organism follows induction of the gene encoding Hpr when such induction is

desirable leading to selective destruction of the Trypanosome and release of the drug or prodrug to the host organism. This allows for production of a stable organism. Therefore, the instant specification provides teaching such that a skilled artisan readily predicts success in making the claimed Trypanosome organisms containing a gene encoding Hpr and their use in drug delivery.

Finally, the instant specification combined with knowledge in the art provides an enabling disclosure for delivering a drug or prodrug to a host cell using the claimed invention. The instant specification teaches methods for creating liposomally packaged therapeutic agents. (p. 18, lines10-12; US Pat Nos. 4,356,167; 4,873,088; and 5,843,475.) Methods are well known in the art for fusing liposomes with eukaryotic cells specifically for the delivery of encapsulated contents into the target cells. Anzar M, et al, *Cytometry* (2002) 49:22-27; Mizoue T, et al, *Int J Pharm* (2002) 237:129-37; Kunisawa J, et al, *Adv Drug Deliv Rev* (2001) 52:177-86; Nakanishi T, et al, *Eur J Immunol* (2000) 30:1740-47. As the delivery of therapeutic agents to eukaryotic cells is well established, these techniques are clearly applicable to delivery of therapeutic agents into a Trypanosome for subsequent delivery to a host organism following lysis of the Trypanosome. As stated in the instant specification, this provides numerous advantages including immune system avoidance, targeted delivery, large molecule delivery, timed release, and elimination of the delivery apparatus. (Table 1.)

Further, the technique of electroporation is well established in the art such that numerous kits and materials for performing it are available on the market. (siPORT™ siRNA Electroporation Kit, Ambion Inc.; US Patent No. 6,586;249; E-Shot™ Standard Electroporation cuvettes, Invitrogen, Inc.) Thus, electroporation is an art recognized method of delivery of even large molecules to eukaryotic cells.

Drugs and prodrugs encompass genes encoding nucleic acid molecules greater than 20 nucleotides in length. *Supra*. Packaging such molecules into Trypanosomes is taught by the instant specification *inter alia* Examples 1-3. Trypanosomes are "transfected with an expression cassette" encoding host genome integration genes and a gene encoding lysosome targeted Hpr. (p. 5, lines 1-24 to p. 6, lines 1-2.) Methods of cell transfection are well known in the art and do not require undue experimentation for a practitioner having ordinary skill in the art.

The Federal Circuit has stated that: "a specification need not disclose what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986). The instant specification and that which is known in the art provide numerous examples of the "conditions under which a process can be carried out." *Genentech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997). Therefore, the subject claimed invention is readily practiced by a skilled artisan without undue experimentation.

In light of the above amendments and remarks, it is respectfully submitted that the instant specification provides teaching of claims 1, 2, 4-9, 11, 13, and 41 so as to enable persons having ordinary skill in the art, or with which it is most nearly connected, to make and use the invention consistent with the requirements of 35 U.S.C. § 112, first paragraph.

Remarks Directed to Rejection of Claims 1, 7, 8, 11, 13,

and 41 under 35 U.S.C. § 112, Second Paragraph

Withdrawal of the rejection of claims 1, 7, 8, 11, 13, and 41 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is respectfully requested for at least the following reasons. Independent claims 1, 11, and 41 are currently amended to include the limitation "a

gene encoding primate Hpr; said gene further comprising an inducible promoter and encoding a lysosomal targeting sequence." This amendment is fully supported by the original disclosure *inter alia* at p. 14, lines 1-4; p. 8, lines 14-16; p. 13, lines 2-6; Table 1; p. 34, lines 3-7.

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, second paragraph. Furthermore, "a claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112 (2004).

The current amendment to independent claims 1 and 11 incorporates the limitation addressed in the specification as originally filed such that such that it is clear how a gene encoding a recombinant lytic factor can be upregulated by a promoter since promoters drive expression of genes. Furthermore, as claim 7 depends from claim 1, and claim 13 depends from claim 11, all limitations of each independent claim are currently incorporated into each corresponding dependent claim.

Claim 41 is currently amended to include the limitations: "A sacromastigophoric organism for delivery of a therapeutic agent obtained by the process comprising the steps of:

culturing sacromastigophoric organisms that have been transfected with an expression vector containing an expression cassette induced by a first exogenous species, the cassette comprising: a first construct having a first inducible promoter controlling expression of primate Hpr; said primate Hpr protein encoded by a gene present in said expression vector; said protein further comprising a lysosomal targeting sequence." This amendment is fully supported by the original disclosure *inter alia* in claim 16 of the application as originally filed and p. 14, lines 1-4;

Example 2, pg. 31-32. As such, claim 41 particularly points out and distinctly claims the inventive subject matter.

In light of the above amendments and remarks, it is respectfully submitted that claims 1, 7, 8, 11, 13, and 41 particularly point out and distinctly claim the subject matter which the Applicant regards as his invention consistent with the requirements of 35 U.S.C. § 112, second paragraph.

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